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**(54) Indole Derivatives**

(57) 3-(Indole-2-carboxamide)quinuclidines of formula I

Ind-CO-NHR I

where

Ind is an unsubstituted 2-indolyl group or a 2-indolyl group substituted once or twice by an alkyl, alkoxy, alkoxycarbonyl and/or alkylthio substituent, each with 1-4 carbon atoms, 7-11 C-aralkyloxy, 1-5 C-acyloxy, 6-10 C-aroyloxy, 6-10 C-aryloxy, trifluoromethyl, cyano, fluoro, chloro, hydroxyl, 1-4 C-alkylsulfonyloxy, 6 -10 C-arylsulfonyloxy, carboxyl and/or methylenedioxy and

R is 3-quinuclidinyl

as well as their physiologically safe salts which have a selective serotonin antagonist effect and can be used as psychopharmaceuticals.

The object of this invention is novel 3-(indole-2-carboxamide)quinuclidine derivatives of formula I

Ind-CO-NHR I

where

Ind is an unsubstituted 2-indolyl group or a 2-indolyl group with one or two substituents in the form of an alkyl, alkoxy, alkoxycarbonyl and/or alkylthio group, each with 1-4 carbon atoms, 7-11 C-aralkyloxy, 1-5 C-acyloxy, 6-10 C-aroyloxy, 6-10 C-aryloxy, trifluoromethyl, cyano, fluoro, chloro, hydroxyl, 1-4 C-alkylsulfonyloxy, 6-10 C-arylsulfonyloxy, carboxyl and/or methylenedioxy, and

R is 3-quinuclidinyl,

as well as their salts.

The object of this invention is to discover novel compounds which can be used to produce pharmaceutical drugs.

It has been discovered that these substances have valuable pharmacological properties and are tolerated well. These effects permit use of these substances for treatment of diseases characterized by an excess of circulating serotonin or by a serotonergic hyperfunction. This includes in particular the treatment of psychoses, nausea and vomiting (such as the side effects of treatment of cancer by chemotherapy or radiation), dementia or other cognitive disorders, migraines and addictive disorders. This also includes use as an anxiolytic, as an antiaggressive or antidepressive drug and as an analgesic. Specifically, these compounds antagonize the action of serotonin on 5-$HT_3$ receptors such as the Bezold-Jarisch reflex induced by serotonin (for methods, see *J. Pharm. Pharmacol.* **40** (1980), 301-302 and *Nature* **316** (1985), 126-131). In addition, these novel compounds displace the substance $^3$H-GR65630, which is known to be a selective 5-$HT_3$ ligand, of homogenized tissue from the endorhinal cortex of the rat (see *Europ. J. Pharmacol.* **159** (1989), 157-164).

Compounds I and their physiologically safe acid addition salts can therefore be used as pharmaceutical active ingredients and as intermediates for the production of other pharmaceutical active ingredients.

Similar compounds are described in *J. Org. Chem.* **40**, 2525-2529 (1975), in *J. Org. Chem.* **38**, 3004-3011 (1973) and in *J. Org. Chem.* **33**, 487-490 (1968). However, no pharmacological effects have been described in any of these cases.

In the Ind group, the 1-4-C-alkyl substituents are preferably methyl or ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *sec*-butyl or *tert*-butyl.1-4-C-Alkoxy is preferably methoxy or ethoxy, *n*-propoxy, isopropoxy, *n*-butoxy, isobutoxy, *sec*-butoxy or *tert*-butoxy, 1-5-C-Acyloxy is

preferably formyloxy or acetyloxy, propanoyloxy, *n*-butanoyloxy, isobutanoyloxy or pivaloyloxy. 1-4-C-Alkylsulfonyloxy is preferably methanesulfonyloxy. 6-10-C-Aryloxy is preferably phenyloxy, 7-11-C-aralkyloxy is preferably benzyloxy, and 6-10-C-aroyloxy is preferably benzoyloxy.

The Ind group preferably denotes an unsubstituted 2-indolyl group or such a group with one or two substituents. If Ind is a substituted 2-indolyl group, then it is preferably substituted in positions 4, 5 and/or 6 and/or alkylated in position 1. Specifically, Ind preferably stands for 2-indolyl, 5-methoxy-2-indolyl, 1- or 5-methyl-2-indolyl, or 4-chloro-2-indolyl or 4-fluoro-2-indolyl. The R group is 3-quinuclidinyl.

The object of this invention is also a method of synthesis of compounds of formula I as well as their salts, characterized in that the compounds of formula II

Ind-CO-X II

where Ind has the meanings given above,

and

X stands for chlorine, bromine, acyloxy, preferably pivaloyloxy, as well as acetyloxy, propionyloxy or butanoyloxy, 1-6-C-alkoxy, preferably methoxy or ethoxy, 7-11-C-aralkyloxy, preferably benzyloxy or 6-10-C-aroyloxy, preferably benzoyloxy, or hydroxy

is reacted with 3-aminoquinuclidine and/or a compound which otherwise corresponds to formula I, but instead of one or more hydrogen atoms, it contains a protective group that can be split off, converting it to a compound of formula I by splitting off this protective group and/or converting one Ind group in a compound of formula I into another Ind group and/or converting a base of formula I into one of its salts by treating it with an acid and/or releasing the base from the salt of a base of formula I by means of a strong base.

Compounds of formula I are otherwise synthesized according to known methods such as those described in the literature (e.g., J. March, *Advanced Organic Chemistry*, 3rd edition, John Wiley & Sons, New York; F. M. Finn et al., *The Proteins*, 3rd edition, vol. II, chapter 2 or Houben-Weyl, *Methods of Organic Chemistry*, Georg Thieme Verlag, Stuttgart), namely under reaction conditions such as those which are known and are suitable for the reactions mentioned above. One can also use known variants that are not specified further here.

Starting materials for the claimed process may also be formed *in situ*, if desired, in such a way that they are not isolated from the reaction mixture but instead are reacted further immediately to form a compound of formula I.

A compound of formula I is synthesized by known methods, such as those used in general to synthesize amides or by the methods of peptide chemistry, preferably by reacting a compound of formula II with 3-aminoquinuclidine or one of its salts in a suitable solvent such as

tetrahydrofuran (THF), dimethyl formamide (DMF), 1,4-dioxane, alcohols such as methanol or ethanol, as well as ethers such as diethyl ether, dichloromethane or mixtures of these solvents at temperatures between 10°C and the respective boiling point of the solvent, optionally with the addition of an activator or a catalyst such as 4-dimethylaminopyridine or N,N'-dicyclohexylcarbodiimide as well as pivalic acid chloride for a period of 0.5 hour to 72 hours.

Compounds of formula I contain at least one asymmetrical carbon atom. They may therefore be used in the form of racemates if there are several asymmetrical carbon atoms, as well as mixtures of several racemates and in different optically active forms. If the compounds have two or more asymmetry centers, they are generally obtained in synthesis as a mixture of racemates from which the individual racemates can be isolated in pure form, e.g., by recrystallization from inert solvents. If desired, the racemates thus obtained can be separated mechanically or chemically into the optical antipodes by essentially known methods. Diasteromers are preferably formed from the racemate by reaction with an optically active separating agent. Suitable separating agents include, for example, optically active acids such as the D- and L-forms of tartaric acid, dibenzoyl tartaric acid, diacetyl tartaric acid, camphor sulfonic acids, mandelic acid, malic acid or lactic acid. The various forms of the diasteromers may be separated by essentially known methods, such as fractional crystallization, and the optically active compounds of formula I can be released from the diastereomers by known methods.

Some of the compounds of formula II are known; the compounds that are not known can be synthesized easily by analogy with the known compounds. For example, N- or O-acylated compounds can be synthesized from their unacylated precursors by reaction with acid anhydrides such as acetic anhydride in basic organic solvents such as pyridine.

Likewise, essentially known methods of derivatization of carboxylic acids may be used to synthesize compounds of formula II.

In addition, a cleavable protective group, in particular a protective group such as benzyloxy that can be split off by hydrogenolysis, may be split off by catalytic hydrogenation from compounds which otherwise correspond to formula I but instead of one or more hydrogen atoms, contain such a protective group, yielding compounds of formula I. In addition, compounds which otherwise correspond to formula I but instead of one or more hydrogen atoms contain a protective group that can be split off by solvolysis such as acyl (e.g., acetyl) or sulfonyl (e.g., methanesulfonyl or toluenesulfonyl) may also be converted to compounds of formula I by solvolysis, in particular by hydrolysis.

Starting materials for solvolysis are accessible, for example, by reaction of 1-Z-Ind-COX with 3-aminoquinuclidine or one of its salts, where Ind has the meanings given above, and Z is a group that can be split off by solvolysis. Thus, compounds of formula I, where the Ind group in position 1 on the indole is an acyl group, preferably an alkanoyl, alkylsulfonyl or arylsulfonyl group, each having up to 10 carbon atoms such as methane sulfonyl, benzene sulfonyl or *p*-toluene sulfonyl in

particular, may be hydrolyzed to the corresponding compounds which are not substituted in position 1, e.g., in an acidic medium, or even better, in a neutral or alkaline medium at temperatures between 0 and 200°C. Preferred bases include sodium hydroxide, potassium hydroxide and calcium hydroxide, sodium carbonate and potassium carbonate or ammonia under conditions under which the acid amide bond is not cleaved. Preferred solvents include water, low alcohols such as methanol or ethanol, ethers such as THF or dioxane, sulfones such as tetramethylene sulfone or mixtures thereof, especially mixtures containing water. Hydrolysis can take place by treating with water alone, especially at the boiling point.

An Ind group in a compound for formula I can be converted to another Ind group if the selected reaction conditions do not destroy the acid amide bond, e.g., by cleaving an ether group, forming the corresponding hydroxyl derivative and/or esterifying a carboxyl group and/or saponifying an ester group and/or splitting off a carboxyl group by decarboxylation. The ether can be split by treating it with a dimethyl sulfide-boron tribromide complex, e.g., in toluene, ethers such as THF or dimethyl sulfoxide or by melting it with pyridine hydrohalides or aniline hydrohalides, preferably pyridine hydrochloride at approximately 150 to 250°C or by treating with diisobutyl aluminum hydride in toluene at approximately 0 to 110°C or by catalytic hydrogenation, e.g., in the presence of palladium carbon in one of the inert solvents mentioned above such as methanol at 0 to 50°C, for example, and 1 to 10 bar, for example. Such an esterification takes place, for example, by treating a solution of the carboxylic acid with an alcohol with the addition of $SOCl_2$ or an agent that splits off water, with an excess of alcohol preferably serving as the solvent. Hydrolysis of carboxylate esters takes place by means of acid or base catalysis in an aqueous solution, which may also contain an inert organic solvent such as dioxane that is miscible with water. Decarboxylation is preferably carried out in an alkaline medium, e.g., in N,N-dimethylaniline at temperatures between 40 and 190°C, preferably between 160 and 190°C.

The resulting base of formula I may be converted to the respective acid addition salts by reacting it with an acid. Acids that supply physiologically safe salts are preferred for this reaction. For example, such acids that may also be used include inorganic acids such as sulfuric acid, hydrohalic acids such as hydrochloric acid or hydrobromic acid, phosphoric acids such as orthophosphoric acid, nitric acid, sulfamic acid, as well as organic acids, specifically aliphatic, alicyclic, araliphatic, aromatic or heterocyclic monobasic or polybasic carboxylic acids, sulfonic acid or sulfuric acids such as formic acid, acetic acid, propionic acid, pivalic acid, diethyl acetic acid, malonic acid, succinic acid, pimelic acid, fumaric acid, maleic acid, lactic acid, tartaric acid, malic acid, benzoic acid, salicylic acid, 2-phenylpropionic acid, citric acid, gluconic acid, ascorbic acid, nicotinic acid, isonicotinic acid, methane sulfonic acid and ethane sulfonic acid, benzene sulfonic acid, *p*-toluene sulfonic acid, naphthalene mono- and disulfonic acids, and lauryl sulfuric acid. Acid addition salts which are not physiologically safe (such as picrates) may be suitable for isolation and purification of the bases of formula I.

If desired, a base of formula I may be released from one of its salts with a strong base such as sodium or potassium hydroxide or sodium or potassium carbonate.

The object of this invention is also the use of compounds for formula I and/or also their physiologically safe salts for production of pharmaceutical preparations, in particular by nonchemical methods, whereby they can be converted to a suitable form of administration together with at least one vehicle or additive and optionally in combination with one or more other active ingredients.

The object of this invention also includes agents, pharmaceutical preparations in particular, containing one or more compounds of formula I and/or their physiologically safe salts. These preparations may be used as pharmaceutical drugs in human and veterinary medicine. Suitable vehicle substances include organic and inorganic substances which are suitable for enteral (e.g., oral), parenteral or topical application and which do not react with these novel compounds; such suitable vehicles include water, vegetable oils, benzyl alcohols, polyethylene glycols, gelatin, carbohydrates such as lactose or starch, magnesium stearate, talc and liquid petrolatum. In particular, tablets, pills, capsules, syrups, liquids, drops or suppositories are suitable for enteral administration, and solutions, preferably oil-based solutions or water-based solutions as well as suspensions, emulsions and implants are suitable for parenteral administration, and creams, ointments, patches or powders are suitable for topical application. These novel compounds may also be lyophilized, and the resulting lyophilizates may be used to prepare injection preparations, for example.

The preparations according to this invention may be sterilized and/or may contain additives such as preservatives, lubricants, stabilizers and/or wetting agents, emulsifiers, salts to influence the osmotic pressure, buffering substances, coloring agents, flavoring agents and/or perfumes. If desired, they may also contain one or more other active ingredients, e.g., one or more vitamins.

Compounds of formula I and their physiologically safe salts may be used for therapeutic treatment of the human or animal body and to combat diseases, in particular diseases characterized by an excess of circulating serotonin or a serotonergic hyperfunction. Such diseases include in particular psychoses, nausea and vomiting, such as the side effects of treatment of tumors with chemotherapy and radiation therapy, as well as dementia and other cognitive disorders, migraines and addictive disorders. In addition, the range of indications also includes anxiolytic, analgesic, antidepressant and antiaggressive effects.

Substances according to this invention are usually administered like known preparations which are available commercially (thioridazine, haloperidol), preferably in doses between approximately 0.2 and 1000 mg, in particular between 0.2 and 100 mg, per dosage unit. The daily dose is preferably between approximately 0.003 and 20 mg/kg body weight. The specific dose for each individual patient, however, depends on a variety of factors, e.g., the efficacy of the specific compound used, the patient's age, weight, general health, sex, diet, time of administration and

method of administration, rate of elimination, drug combination and severity of the respective disease for which this treatment is used. Oral administration is preferred.

Examples

In the examples which follow, the phrase "conventional work-up" has the following meaning: water is added if necessary, extraction is performed with ethyl acetate or ether, the active ingredient is isolated, the organic phase is dried over sodium sulfate, filtered, evaporated and purified by chromatography on silica gel and/or by crystallization. Temperatures are given in degrees Celsius.

The melting points refer to the free bases, unless otherwise indicated.

**Example 1**

An equimolar amount of pivalic acid chloride and 2 mL pyridine are added to a solution of 2.4 g indole-2-carboxylic acid in 70 mL THF. Then at room temperature, 3.1 g 3-aminoquinuclidine in 10 mL THF is added, and the mixture is boiled for three hours. After a conventional work-up, this yields indole-2-carboxylic acid N-(quinuclidin-3-yl)amide, m.p. 178-180°C.

By analogy, by reacting 3-aminoquinuclidine

with 5-methylindole-2-carboxylic acid, this yields 5-methylindole-2-carboxylic acid N-(quinuclidin-3-yl)amide,

m.p. 163-165°C;

with 6-methoxyindole-2-carboxylic acid, this yields 6-methoxyindole-2-carboxylic acid N-(quinuclidin-3-yl)amide,

**with 4-benzyloxyindole-2-carboxylic acid, this yields 4-benzyloxyindole-2-carboxylic acid N-(quinuclidin-3-yl)amide,**

with 5-methoxyindole-2-carboxylic acid, this yields 5-methoxyindole-2-carboxylic acid N-(quinuclidin-3-yl)amide,

m.p. 250-252°C,

with 4-fluoroindole-2-carboxylic acid, this yields 4-fluoroindole-2-carboxylic acid N-(quinuclidin-3-yl)amide,

**m.p. 255-257°C,**

with 5-fluoroindole-2-carboxylic acid, this yields 5-fluoroindole-2-carboxylic acid N-(quinuclidin-3-yl)amide,

**m.p. 316-318°C,**

with 1-ethylindole-2-carboxylic acid, this yields 1-ethylindole-2-carboxylic acid N-(quinuclidin-3-yl)amide,

with 5-ethoxyindole-2-carboxylic acid, this yields 5-ethoxyindole-2-carboxylic acid N-(quinuclidin-3-yl)amide,

with 6-ethoxyindole-2-carboxylic acid, this yields 6-ethoxyindole-2-carboxylic acid N-(quinuclidin-3-yl)amide,

with 7-ethoxyindole-2-carboxylic acid, this yields 7-ethoxyindole-2-carboxylic acid N-(quinuclidin-3-yl)amide,

with 5-cyanoindole-2-carboxylic acid, this yields 5-cyanoindole-2-carboxylic acid N-(quinuclidin-3-yl)amide,

with 6-cyanoindole-2-carboxylic acid, this yields 6-cyanoindole-2-carboxylic acid N-(quinuclidin-3-yl)amide,

with 7-cyanoindole-2-carboxylic acid, this yields 7-cyanoindole-2-carboxylic acid N-(quinuclidin-3-yl)amide,

with 4-chloroindole-2-carboxylic acid, this yields 4-chloroindole-2-carboxylic acid N-(quinuclidin-3-yl)amide,

m.p. 240-242°C,

with 5-chloroindole-2-carboxylic acid, this yields 4-chloroindole-2-carboxylic acid N-(quinuclidin-3-yl)amide,

with 6-chloroindole-2-carboxylic acid, this yields 6-chloroindole-2-carboxylic acid N-(quinuclidin-3-yl)amide,

with 5,6-dimethoxyindole-2-carboxylic acid, this yields 5,6-dimethoxyindole-2-carboxylic acid N-(quinuclidin-3-yl)amide,

with 5,6-methylenedioxyindole-2-carboxylic acid, this yields 5,6-methylenedioxyindole-2-carboxylic acid N-(quinuclidin-3-yl)amide,

with 4,5,6-trimethoxyindole-2-carboxylic acid, this yields 4,5,6-triimethoxyindole-2-carboxylic acid N-(quinuclidin-3-yl)amide,

with 5-trifluoromethylindole-2-carboxylic acid, this yields 5-trifluoromethylindole-2-carboxylic acid N-(quinuclidin-3-yl)amide,

with 6-trifluoromethylindole-2-carboxylic acid, this yields 6-trifluoromethylindole-2-carboxylic acid N-(quinuclidin-3-yl)amide,

**with 5-benzyloxyindole-2-carboxylic acid, this yields 5-bnzyloxyindole-2-carboxylic acid N-**

**(quinuclidin-3-yl)amide,**

m.p. 283-284°C,

with 5-benzylindole-2-carboxylic acid, this yields 5-benzyindole-2-carboxylic acid N-(quinuclidin-3-yl)amide,

with 6-benzylindole-2-carboxylic acid, this yields 6-benzyindole-2-carboxylic acid N-(quinuclidin-3-yl)amide,

with 6-benzyl-1-methylindole-2-carboxylic acid, this yields 6-benzyl-1-methylindole-2-carboxylic acid N-(quinuclidin-3-yl)amide,

with 6-chloro-1-methylindole-2-carboxylic acid, this yields 6-chloro-1-methylindole-2-carboxylic acid N-(quinuclidin-3-yl)amide,

with 6-cyano-1-methylindole-2-carboxylic acid, this yields 6-cyano-1-methylindole-2-carboxylic acid N-(quinuclidin-3-yl)amide,

with 1-methylindole-2-carboxylic acid, this yields 1-methylindole-2-carboxylic acid N-(quinuclidin-3-yl)amide,

m.p. 182-184°C.

with 7-benzylindole-2-carboxylic acid, this yields 7-benzylindole-2-carboxylic acid N-(quinuclidin-3-yl)amide,

with 6-ethoxyl-1-methylindole-2-carboxylic acid, this yields 6-ethoxy-1-methylindole-2-carboxylic acid N-(quinuclidin-3-yl)amide,

**with 6-benzyloxyindole-2-carboxylic acid, this yields 6-benzyloxyindole-2-carboxylic acid N-(quinuclidin-3-yl)amide,**

**with 7-benzyloxyindole-2-carboxylic acid, this yields 7-benzyloxyindole-2-carboxylic acid N-(quinuclidin-3-yl)amide,**

m.p. 268-269°C.

with 5-cyano-1-methylindole-2-carboxylic acid, this yields 5-cyano-1-methylindole-2-carboxylic acid N-(quinuclidin-3-yl)amide,

with 6-propoxyindole-2-carboxylic acid, this yields 6-propoxyindole-2-carboxylic acid N-(quinuclidin-3-yl)amide,

with 7-fluoroindole-2-carboxylic acid, this yields 7-fluoroindole-2-carboxylic acid N-(quinuclidin-3-yl)amide,

with 4-trifluoromethylindole-2-carboxylic acid, this yields 4-trifluoromethylindole-2-carboxylic

acid N-(quinuclidin-3-yl)amide,

with 5-ethylindole-2-carboxylic acid, this yields 5-ethylindole-2-carboxylic acid N-(quinuclidin-3-yl)amide,

with 6-*tert*-butylindole-2-carboxylic acid, this yields 6-*tert*-butylindole-2-carboxylic acid N-(quinuclidin-3-yl)amide,

with 6-acetoxy-1-methylindole-2-carboxylic acid, this yields 6-acetoxy-1-methylindole-2-carboxylic acid N-(quinuclidin-3-yl)amide.

**Example 2**

300 mg 5-hydroxyindole-2-carboxylic acid N-(quinuclidin-3-yl)amide is dissolved in 20 mL pyridine and then mixed with 8 mL acetic anhydride while cooling. Next it is stirred for one hour at room temperature and worked up as usual, yielding 5-acetoxyindole-2-carboxylic acid N-(quinuclidin-3-yl)amide.

By analogy, by reacting the 4-, 5- or 6-hydroxyindole-2-carboxylic acids with the corresponding carboxylic acid anhydrides, this yields

5-pivaloyloxyindole-2-carboxylic acid N-(quinuclidin-3-yl)amide,

6-pivaloyloxyindole-2-carboxylic acid N-(quinuclidin-3-yl)amide,

6-butanoyloxyindole-2-carboxylic acid N-(quinuclidin-3-yl)amide,

5-butanoyloxyindole-2-carboxylic acid N-(quinuclidin-3-yl)amide,

4-propanoyloxyindole-2-carboxylic acid N-(quinuclidin-3-yl)amide,

5-propanoyloxyindole-2-carboxylic acid N-(quinuclidin-3-yl)amide,

6-propanoyloxyindole-2-carboxylic acid N-(quinuclidin-3-yl)amide,

4-methanesulfonyloxyindole-2-carboxylic acid N-(quinuclidin-3-yl)amide,

5-methanesulfonyloxyindole-2-carboxylic acid N-(quinuclidin-3-yl)amide,

6-methanesulfonyloxyindole-2-carboxylic acid N-(quinuclidin-3-yl)amide,

5-propanoyloxy-1-methylindole-2-carboxylic acid N-(quinuclidin-3-yl)amide,

4-methanesulfonyloxy-1-methylindole-2-carboxylic acid N-(quinuclidin-3-yl)amide,

5-methanesulfonyloxy-1-methylindole-2-carboxylic acid N-(quinuclidin-3-yl)amide and

5-acetoxy-1-methylindole-2-carboxylic acid N-(quinuclidin-3-yl)amide.

**Example 3**

**0.5 g 7-benzyloxyindole-2-carboxylic acid N-(quinuclidin-3-yl)amide (m.p. 268-269°C) is dissolved in 40 mL methanol. Then after adding 0.2 g palladium carbon (5%), the mixture is hydrogenated for a period of one hour at room temperature**. The hydrogenation solution is then concentrated and worked up as usual, yielding 7-hydroxyindole-2-carboxylic acid N-(quinuclidin-3-yl)amide.

Similarly, by hydrogenation

of 5-benzyloxyindole-2-carboxylic acid N-(quinuclidin-3-yl)amide

**(m.p. 283-284°C)**

this yields

**5-hydroxyindole-2-carboxylic acid N-(quinuclidin-3-yl)amide,**

by hydrogenation of 6-benzyloxyindole-2-carboxylic acid N-(quinuclidin-3-yl)amide, this yields 6-hydroxyindole-2-carboxylic acid N-(quinuclidin-3-yl)amide

and

by hydrogenation of 4-benzyloxyindole-2-carboxylic acid N-(quinuclidin-3-yl)amide, this yields 4-hydroxyindole-2-carboxylic acid N-(quinuclidin-3-yl)amide.

**Example 4**

2.7 g 5-methylindole-2-carboxylic acid is dissolved in 100 mL THF at room temperature with the addition of 3.0 g dicyclohexyl carbodiimide (DCC) and then mixed with 3.2 g 3-aminoquinuclidine suspended in 20 mL THF. Next the mixture is stored for 6 hours at 40°C and then worked up as usual, yielding 5-methylindole-2-carboxylic acid N-(quinuclidin-3-yl)amide.

The following examples concern pharmaceutical preparations containing substances of formula I or one of their acid addition salts:

**Example A: Tablets**

A mixture of 1 kg 4-chloroindole-2-carboxylic acid N-(quinuclidin-3-yl)amide, 4 kg lactose, 1.2 kg potato starch, 0.2 kg talc and 0.1 kg magnesium stearate is pressed to form tablets in the usual manner so that each tablet contains 10 mg active ingredient.

**Example B: Coated pills**

By analogy with Example A, tablets are pressed and then coated with a coating of sucrose, potato starch, talc, gum tragacanth and coloring agent in the usual manner.

**Example C: Capsules**

A 2 kg batch of 5-methoxyindole-2-carboxylic acid N-(quinuclidin-3-yl)amide is used to fill hard gelatin capsules in the usual manner, so that each capsule contains 20 mg active ingredient.

**Example D: Ampules**

A solution of 1 kg indole-2-carboxylic acid N-(quinuclidin-3-yl)amide in 60 L double-distilled water is filtered under sterile conditions, bottled in ampules, lyophilized under sterile conditions and sealed under sterile conditions. Each ampule contains 10 mg active ingredient.

Tablets, coated pills, capsules and ampules containing another compound of formula I and/or one or more physiologically safe acid addition salts of a compound of formula I can be produced by similar methods.

**Patent Claims**

**1.** 3-(Indole-2-carboxamide)quinuclidines of formula I

Ind-CO-NHR I

where

Ind is an unsubstituted 2-indolyl group or a 2-indolyl group having one or two substituents in the form of an alkyl, alkoxy, alkoxycarbonyl and/or alkylthio each with 1-4 carbon atoms, 7-11 C-aralkyloxy, 1-5 C-acyloxy, 6-10 C-aroyloxy, 6-10 C-aryloxy, trifluoromethyl, cyano, fluoro, chloro, hydroxyl, 1- 4 C-alkylsulfonyloxy, 6-10 C-arylsulfonyloxy, carboxyl and/or methylene dioxy, and

R is 3-quinuclidinyl,

as well as their salts.

**2.** a) 4-Chloroindole-2-carboxylic acid N-(quinuclidin-3-yl)amide,

b) 5-methoxyindole-2-carboxylic acid N-(quinuclidin-3-yl)amide,

c) indole-2-carboxylic acid N-(quinuclidin-3-yl)amide,

d) 1-methylindole-2-carboxylic acid N-(quinuclidin-3-yl)amide,

e) 5-methylindole-2-carboxylic acid N-(quinuclidin-3-yl)amide,

f) 4-fluoroindole-2-carboxylic acid N-(quinuclidin-3-yl)amide.

**3.** A method of synthesis of compounds of formula I according to claim 1, as well as their salts, characterized in that compound of formula II

Ind-CO-X II

where the Ind group has the meanings given in claim 1, and X stands for Cl, Br, acyloxy, alkoxy, each having 1-6 carbon atoms, aralkyloxy with 7 to 11 carbon atoms, or an

aroyloxy, each with 6 to 10 carbon atoms, or a hydroxyl is reacted with 3-aminoquinuclidine and/or a compound which otherwise corresponds to formula I but instead of containing one or more hydrogen atoms, it has a protective group that can be split off, converting it to a compound of formula I by splitting off this protective group and/or converting one Ind group in a compound of formula I into another Ind group and/or converting a base of formula I into one of its salts by treating it with an acid.

4. The method of synthesis of a pharmaceutical preparation, characterized in that a compound of formula I according to claim 1 and/or one of its physiologically safe salts is converted to a suitable form of administration together with at least one solid, liquid or semiliquid vehicle or additive.

5. A pharmaceutical preparation characterized by a content of at least one compound of formula 1 according to claim 1 and/or one its physiologically safe salts.

6. Use of a compound of formula I according to claim 1 and/or one of its physiologically safe salts to combat diseases.

7. Use of a compound of formula I according to claim 1 and/or one of its physiologically safe salts to produce pharmaceutical drugs.

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